REMARKS:

Claims 9-18, 21-38, and 41 are pending. Claims 1-8, 19, and 20 have been withdrawn. Claims 37 and 38 have been allowed per page 5 of the Office Action mailed September 7, 2007. Claims 39 and 40 have been cancelled. Claim 41 is new, and does not add new matter. Support for claim 41 may be found in Example 1 of the published application.

I. 35 USC §103 rejection

Reconsideration is requested of the rejection of claims 9-18 and 21-38 under 35 USC §103(a) over Klinkenberg et al. in view of Griffith et al. in combination with US patent No. 6,110,744 (Fang et al.; hereinafter the '744 patent).

(a) Independent Claim 9 and Dependent Claims 10-18

Claim 9 is directed to a method of decreasing cell proliferation. The method comprises contacting, in vitro, a eukaryotic cell comprising a wild-type MetAP2 with a composition comprising an isolated polynucleotide. The polynucleotide encodes a variant eukaryotic MetAP2 that *lacks aminopeptidase activity*, comprises a translation domain, and *possesses dominant negative MetAP2 activity*. The dominant negative activity of the variant MetAP2 decreases the proliferation of the cell.

Klinkenberg et al. disclose a dominant negative MetAP1 variant. The variant has a *different substrate specificity* than wild-type MetAP1, but *still maintains catalytic activity*.[1] Klinkenberg et al., however, does not disclose a dominant negative MetAP2. In particular, Klinkenberg et al. does not disclose a variant MetAP2 that *lacks aminopeptidase activity*, and *possesses dominant negative MetAP2 activity*, as required by claim 9. Nor does the Klinkenberg reference disclose decreasing cell proliferation with a dominant negative MetAP2 variant.

[1] See Tables II and III of the Klinkenberg reference.

Griffith et al. discloses that the "covalent modification of His231 [of MetAP2] by fumagillin, ovalicin, and TNP-40 serves to irreversibly block the active site of MetAP2, preventing substrate binding and catalysis." The authors of the Griffith reference engineered several mutations in the active site of MetAP2, and expressed the mutated proteins using a baculovirus expression system. Importantly, Griffith et al. used fumagillin, or a similar drug, to impede cell proliferation. Griffith et al. did not disclose, mention, or suggest inhibiting cell proliferation by anything other than a fumagillin-like drug. Specifically, Griffith et al. does not disclose decreasing cell proliferation with a dominant negative MetAP2, as required by claim 9.

The '744 patent discloses adenovirus vectors comprising, in part, a CMV promoter. The vectors may be used to produce an infectious, conditionally replication-defective adenovirus particle. The '744 patent does not disclose variants of MetAP2. Similar to the Griffith reference, the '744 patent also does not disclose decreasing cell proliferation with a dominant negative MetAP2, as required by claim 9.

Three criteria must be present to establish a prima facie case of obviousness. First, the prior art reference(s) *must* teach or suggest ***all*** *the claim limitations*. Second, there *must* be some suggestion or motivation in the knowledge generally available to one of ordinary skill in the art to modify the reference. Third, there *must* be a reasonable expectation of success. ***Not one of these three criteria is satisfied by the Klinkenberg reference, either alone or in combination with the Griffith reference and the '744 patent.***

Neither Klinkenberg et al., Griffith et al. nor the '744 patent teach or suggest every claim limitation of claim 9. Specifically, Klinkenberg et al., Griffith et al., and the '744 patent **DO NOT** disclose or suggest a method of decreasing cell proliferation with a variant MetAP2 that has dominant negative activity. Instead, the Klinkenberg article discloses a dominant negative MetAP1 variant that still possesses catalytic activity. Claim 9 of the present application, however, specifically requires a MetAP2 variant, and the MetAP2 variant must lack

aminopeptidase activity. The Klinkenberg reference does not disclose these limitations.

The Griffith patent focuses only on using a fumagillin-like drug to modulate cell proliferation. It also does not disclose or suggest a method of decreasing cell proliferation with a variant MetAP2 that has dominant negative activity, as required by Claim 9. In addition, as stated above, the '744 patent does not disclose variants of MetAP2.

Consequently, because none of the three cited references teach or suggest every claim limitation of Claim 9, these references, whether taken individually or combined, do not render claim 9 obvious.

Additionally, there is no suggestion or motivation in the knowledge generally available to one of ordinary skill in the art to modify the Klinkenberg reference, the Griffith reference, or the '744 patent such that claim 9 is rendered obvious. The Klinkenberg reference discloses a dominant negative MetAP1 variant that possesses catalytic activity (see page 196, second column, of the Klinkenberg reference). As stated above, the Klinkenberg article ***does not teach a MetAP2 variant***. In addition, claim 9 requires that the MetAP2 variant lack aminopeptidase activity. However, the MetAP1 variant of the Klinkenberg reference *maintains* aminopeptidase activity.[2] Hence, it would not have been apparent, from the Klinkenberg reference, that a dominant negative variant of MetAP2 that lacked catalytic activity could be used to decrease cell proliferation.

This is true even in light of the Griffith reference. The Griffith reference focuses on the mechanism of a known inhibitor of MetAP2 function. Importantly, in order to modulate cell proliferation, the Griffith reference teaches that you have to use a fumagillin-like drug. The reference discloses that a MetAP2 protein with alanine instead of histidine at position 231 lacks catalytic activity. But this is markedly different from dominant negative activity. For a comparison of the differences between a catalytically inactive protein, a drug-inactivated protein,

[2] See Tables II and III of the Klinkenberg reference.

and a dominant negative protein when added to an assay comprising wild-type protein, see Table 1.

Table 1:

Added element	**Total amount of protein**	**Does wild-type protein posses an active catalytic site?**	**Measured result of wild-type protein activity**
Catalytically inactive protein	Increases	Yes	Stays the same
Drug capable of inactivating protein	Stays the same	No	Decreases
Dominant Negative Protein	Increases	Yes	Decreases

If a catalytically inactive protein is added to an assay that comprises wild-type protein, then one skilled in the art would expect that you would merely increase the total protein in the cell without effecting the measured result of the wild-type protein's activity. In stark contrast, the addition of a dominant negative protein to an assay that comprises wild-type protein not only increases total protein level, but *decreases the measurable enzymatic activity of the wild-type protein, in a dose-dependant fashion.*

Furthermore, if a fumagillin-like drug is added to an assay comprising wild-type MetAP2 protein, the drug will block the active site of the protein, therefore decreasing the measured result of wild-type protein activity. However, if you add

a dominant negative MetAP2 to an assay comprising wild-type MetAP2 protein, you will not affect the wild-type protein's active site, but you will decrease the activity of the wild-type MetAP2. In the present invention, this is because the dominant negative MetAP2 is bound to ribosomes, excluding the wild-type MetAP2, and therefore impeding the wild-type MetAP2 protein's activity.

The Griffith article focuses on the first two rows of Table 1, namely a catalytically inactive MetAP2 and a drug capable of inactivating MetAP2 (fumagillin). The differences highlighted in Table 1 between a catalytically inactive protein and a dominant negative protein show that, to one of skill in the art, a catalytically inactive protein is not necessarily and inevitably a dominant negative protein.[3] Therefore, there was no suggestion or motivation in the knowledge generally available to one of ordinary skill in the art to modify the Griffith reference so as to use a variant MetAP2, with dominant negative activity, to modulate cell proliferation.

The Office has stated that "it would have been obvious for one of ordinary skill in the art to substitute the MetAP1 mutant gene producing an catalytically inactive enzyme as taught by Klinkenberg with a MetAP2 mutant gene producing an catalytically inactive enzyme as taught by Griffith and dominant negatively inhibit the cell proliferation in vitro."[4] The Office is mistaken, however. Klinkenberg does not, as the Office asserts, disclose a "catalytically inactive enzyme, " but instead, discloses an enzyme that maintains catalytic activity. For instance, see Tables II and III of the Klinkenberg reference. In addition, assuming for the sake of argument that Klinkenberg did disclose an inactive enzyme, there is no suggestion from Klinkenberg or Griffith that a mutation in MetAP1 can be "substituted" into MetAP2 with the same result.

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[3] See declaration of Dr. Chang filed 6/21/07: "A skilled researcher in the art knows that a catalytically inactive variant is not synonymous with a dominant negative variant, and that it would not be obvious, likely, or intuitive that a catalytically inactive variant would possess dominant negative activity. Stated another way, dominant negative activity does not necessarily and inevitably flow from a catalytically inactive variant."

[4] Office action mailed July 9, 2008, page 4.

Lastly, there would have been no reasonable likelihood of success to modify the Klinkenberg reference or the Griffith article to use a dominant negative variant that is catalytically inactive to modulate cell proliferation, because, as shown in Table 1, with a catalytically inactive protein, one of skill in the art would have predicted no change in wild-type protein activity, and therefore, no change in cell proliferation.

In summary, the Klinkenberg article, the Griffith article, and the '744 patent **DO NOT** disclose the claim limitations of claim 9-18 and 21-24 of decreasing cell proliferation with a dominant negative MetAP2. Additionally, there would have been no motivation or suggestion in the knowledge generally available to one skilled in the art to use the catalytically inactive MetAP2 as a dominant negative MetAP2. Furthermore, there would have been no reasonable likelihood of success because one skilled in the art would not expect a catalytically inactive protein to modulate wild-type protein activity, and therefore, cell proliferation. Consequently, not one of the three requirements for a prima facie case of obviousness is met by the Klinkenberg reference, either alone or in combination with the Griffith reference and the '744 reference. Therefore, these references cannot render claims 9-18 and 21-24 obvious.

(b) Independent Claim 25 and Dependent Claims 26-36

Similarly, independent claim 25 and dependent claims 26-36 are also directed to a method of decreasing cell proliferation, and incorporate the limitations discussed above with respect to claim 9. Hence, claims 25-36 are also not rendered obvious in light of Klinkenberg et al., Griffith et al., and the '744 patent.

(c) Independent Claim 37 and Dependent Claim 38

Independent claim 37 and dependent claim 38 have previously been allowed by the Examiner in the Office Action dated September 7, 2007. Claim 37 encompasses a method for decreasing cell proliferation. The method comprises contacting a yeast cell comprising a wild-type MetAP2 with a composition

comprising an isolated polynucleotide. The polynucleotide encodes a variant yeast MetAP2 that has the amino acid sequence of SEQ ID NO:8 and possesses dominant negative MetAP2 activity. The dominant negative activity of the variant MetAP2 decreases the proliferation of the cell. As detailed above with respect to claim 9, Klinkenberg et al., Griffith et al., and the '744 patent do not disclose or suggest the use of a dominant negative MetAP2 variant to decrease cell proliferation. Consequently, claims 37 and 38 are not rendered obvious in light of Klinkenberg et al., Griffith et al., and the '744 patent.

(d) New claim 41

New claim 41 is directed to a method for inhibiting the function of wild-type eukaryotic MetAP2. The method comprises contacting wild-type MetAP2 with a composition comprising an isolated polynucleotide, wherein the polynucleotide encodes a variant eukaryotic MetAP2 that lacks aminopeptidase activity, comprises a eukaryotic translation domain, and possesses dominant negative MetAP2 activity. The dominant negative activity of the variant MetAP2 inhibits the function of wild-type eukaryotic MetAP2. Klinkenberg et al., Griffith et al., and the '744 patent do not disclose, teach, or suggest a method of using a dominant negative variant of MetAP2 that lacks aminopeptidase activity to inhibit the function of wild-type MetAP2. Hence, claim 41 is not rendered obvious in light of Klinkenberg et al., Griffith et al., and the '744 patent.

In light of the above discussion, applicants respectfully request withdrawal of the §103(a) rejection of claims 9-18 and 21-38 in light of Klinkenberg et al., Griffith et al., and the '744 patent.

II.CONCLUSION

In light of the foregoing, applicants request entry of the claim amendments, withdrawal of the claim rejections, and solicit an allowance of the claims. The Examiner is invited to contact the undersigned attorney should any issues remain unresolved.

Respectfully submitted,

Polsinelli Shalton Flanigan Suelthaus PC

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By: /Rebecca C. Riley-Vargas/

Rebecca C. Riley-Vargas, Reg. No. 60,046
110 South Fourth Street, Suite 1100
St. Louis, MO 63102
Phone – 314-889-8000
Fax – 314-231-1776
Attorney